Research Square

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Catechin and Curcumin interact with corona (2019-nCoV/SARS-CoV2) viral S protein and ACE2 of human cell membrane: insights from Computational study and implication for intervention

Atala B. Jena
Centre Of Excellence In Integrated Omics and Computational Biology, Utkal University
Namrata Kanungo
Post Graduate Department of Biotechnology, Utkal University
Vinayak Nayak
Post Graduate Department of Biotechnology, Utkal University
G.B.N. Chainy
Post Graduate Department of Biotechnology, Utkal University
Jagneshwar Dandapat (jd.biotech@utkaluniversity.ac.in)
Centre Of Excellence In Integrated Omics and Computational Biology and Post Graduate Department of Biotechnology, Utkal University

Research Article

Keywords: Coronavirus, Curcumin, Catechin, Molecular Docking, Simulation, polyphenols

Posted Date: April 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-22057/v1

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Version of Record: A version of this preprint was published on January 21st, 2021. See the published version at https://doi.org/10.1038/s41598-021-81462-7.

Abstract

The recent outbreak of the coronavirus (2019n-CoV) is an unprecedented threat for human health throughout the globe. In this regards development of a suitable intervention is the need of the hour. The viral spike protein (S-Protein) and the cognate host cell receptor ACE2 can prove to be effective. Here, through computational approaches we have reported two polyphenols, Catechin and Curcumin which have dual binding affinity i.e both the molecule binds to viral S-protein and as well as ACE2. Catechin binds with S-protein and ACE2 with binding energy of -10.5 Kcal/mol and -8.9 Kcal/mol, respectively. Catechin binds with a greater affinty than that of curcumin which has a binding energy of -7.9Kcal/mol and - 7.8Kcal/mol for S-protein and ACE2, respectively. While curcumin gets bound directly to receptor binding domain (RBD) of viral S-protein, catechin binds to near proximity of RBD sequence of S-protein. Molecular simulation study demonstrates that curcumin directly binds with RBD site of S-protein during 40-100ns. In contrast, catechin binds with S-protein near the RBD site and causes fluctuation in the amino acids present in the RBD and it's near proximity. In conclusion, this computational study for the first time predicts the possibility of above two polyphenols, for therapeutic/preventive intervention.

Introduction

Corona viruses (2019-nCoV/SARS-CoV2)belonging to family *Coronaviridae,* are single stranded, enveloped, positive sense RNA viruses mostly infecting (birds and mammalsand a matter of global concern[1,2]. WHO declared it pandemic due to its high rate of transmission and unavailability of specific vaccine or medication to treat it3.Phylogenetically SARS CoV2 belongs to order *Nidovirales*[4]and grouped under Betacoronavirus, with a genome size of ~30 kilobases, which codes for different structural and accessory proteins[4,5]. The general morphology of coronavirus includes different structural proteins such as spike (S) protein, envelope (E) protein, membrane (M) protein and the nucleocapsid (N) protein[6]. Corona virus invades human cells through binding of its distinct surface spike protein (glycoprotein in nature) with a receptor protein (s) present on the membrane of human cells. This mediates receptor attachment and viral-host cell membrane fusion (Fig. 1). The S protein is a transmembrane protein with N- exo and C—endo terminals. The N terminal S_1 subunit contains Receptor Binding Domain (RBD) while the C terminal S_2subunit induces membrane fusion[7] (Suppl. Fig. S1). Fusion of virus with human cells is resulted due to the binding of S_1 subunit of viral protein S to human cell receptors[7,8]. On the other hand, consequent upon endocytosis of the virus, the S_2 subunit which is characterised by Heptad Repeats (HR) regions that assembles into an intra-hairpin helical structure with six helix bundle promotes the membrane fusion process inside the host cell[9,10]. In a very recent study, Lu et al., 2020 have observed that external subdomain of S-glycoprotein of 2019-NCoV RBD is more similar to that of SARS-CoV[2], which suggests that this virus also target Angiotensin Converting Enzyme 2 (ACE2), a monomeric membrane bound protein of human cells [11]. Therefore, it is presumed that ACE2, the cognate receptor of corona virus present in the host cells can also be a specific target to prevent the viral entry[12].

Several recent studies have suggested that natural polyphenolic compounds like catechins (GTCs; from green tea) and curcumin (diferuloylmethane; from turmeric)have antiviral activities against a broad spectrum of viruses such as Human Immunodeficiency Virus (HIV), Herpes Simplex Virus, Influenza Virus, Hepatitis B and C Viruses (HBV and HCV respectively)[13], Adenovirus, Zikavirus[14], Chikungunya virus (CHIKV)[15]. Diverse mechanisms have been suggested to explain the antiviral activities of both the polyphenoliccompounds.For example, GTCs have been documented to be a potential suppresser of viral entry and its replication[16–20]while curcumin has been demonstrated as a potent inhibitor of monophosphate dehydrogenase a rate limiting enzyme in the de novo synthesis of guanine nucleotide[21]. Further, it has also been observed that GTCs and curcumininhibit the expression of ACE2,as evident from animal studies[22,23].

Although catechin and curcumin have been reported to bind with various proteins of viral and human origin, till date no data is available for their interaction with S protein of the coronavirus and its cognate receptor, ACE 2 of host cell. With this back drop, the present study has been designed to examine interaction of catechin and curcumin with S protein of the virus and its cognate receptor ACE 2 of host cell employing computational methods. Computational approaches (Molecular docking and simulation) are the first and foremost choice of scientists to prophecy apparent binding modes and affinities of ligands for macromolecules before experimental studies which are indeed expensive and time consuming. In addition, improvement of speed, reliability and accuracy of computational docking methods in last few years made it a suitable choice to design structure-based drugs. The present study incorporates results of molecular docking of catechin and curcumin with the Protein S of corona virus as well as the comparative binding affinity of the above phytochemicals with ACE 2 of host cell a cognate receptor for viral S-protein.

Materials And Methods

Sequence analysis

The cryo EM structure of 2019-nCoV S-protein (PDB ID—6vsb) and X-Ray diffraction structure of ACE2 (PDB ID—1r42) with resolution of 3.46 A^0 and 2.2 Å respectively, were retrieved from PDB database. The FASTA sequence of S-protein of 2019-nCoV, HCoV- 229E, MERS-CoV, HCoV-NL63, SARS-CoV were also retrieved for multiple sequence alignment analysis. The alignment results of 2019-nCoVportrayed that all the three chains of S-protein have identical amino acid sequences. Therefore, only one chain was taken for secondary structureanalysisand prediction of physicochemical properties.

Phylogenetic analysis

FASTA sequence of S-protein was retrieved from PDB database and evolutionary analysis of genetic distance and diversity were conducted by MEGA-X. Analysis was accomplished using the Substitution Model Jones-Taylor-Thornton (JTT)[24] and standard error estimate(s) were obtained by a bootstrap

procedure (1000 replicates). The phylogenetic tree was produced by Maximum Likelihood statistical method.

Molecular docking analysis between S-protein and ACE2 withCatechin and Curcumin

Evaluation of binding free energy of S-protein and ACE2 with catechin and curcumin was done through molecular docking program AutoDock4. The canonical SMILES id of catechin (Catechin-Gallocatechin-Catechin) and curcumin were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Conversion to 3D structures were done using CHIMERA programme. Binding affinity of S-protein and ACE2 with catechin and curcumin were examined using Vina1.1.2. Various parameters such as binding affinity, receptors interacting atom, receptor pocket atom, receptor ligand interaction site, atomic contact energy (ACE) and side amino acid residues were studied to recognise the binding site of S-protein and ACE2. The results of docking were visualised and analysed by Discovery Studio Visualizer.

Molecular simulation

Virtual Screening and energy minimization

The chemically unstandardized 2D structures of ligands, curcumin and catechin were taken up from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Ligand files can be switched to properly standardised and extrapolated 3D structures by LigPep. These structures can be screened virtually. LigPrep plays a major role in conversion of 3D structures to consequently lower energy structures which can be used by Glide and QikProp programs. This minimisation of structures is done using OPLS3e force field. Each input structure generates multiple output structures due to different stereochemistry, protonation states, tautomer's and ring conformations. In the ligand output file specifications are made for production of one low energy ring conformation per ligand.. Grid-based Ligand Docking with

Energetics (GLIDE) module in Schrodinger software was used for the formation of S-protein- Curcumin and S-protein- Cathechin complex. Desmond software was used for carrying out molecular dynamics simulations, Root Mean Square Deviations (RMSD) and atomic fluctuation through Root Mean Square Fluctuation (RMSF) studies. For conducting explicit solvent simulations with periodic marginal conditions, different tools such as cubic, orthorhombic, truncated octahedron, rhombic dodecahedron and other arbitrary simulation boxes are used.

Here in this study, MD simulations were conducted notably for the top two identified hits to analyse the stability of the ligand receptor complex for 100ns. Stability of docked complexes 2019-nCoV spike glycoprotein-Curcuminand 2019-nCoV spike glycoprotein-Catechinare simulated till 100ns simulation time by performing Molecular Dynamics (MD) simulations using system builder of Desmond implemented in Maestro12.0 with OPLS–3 force field.Neutralisation of the docked complex was done by

the addition of 4 Na^+ ions and 1.137 mMconcentration of Na^+ ions into the system for S-protein and curcumin. Similarly, 6 Na^+ ions and 1.706 mM concentration of Na^+ ions for neutralisation of S-protein and Catechin.

The decrease in the potential energy during the 100ns in case of both Catechin- S-protein, Curcumin- S-proteincomplexes revealed that the system is stable. Analysis of different conformations acquired over the simulation period of 100ns is done. For the computation of average change in the displacement of selected atoms in a particular frame with respect to reference frame, Root mean square deviation (RMSD) is estimated for the protein and ligand for 100 ns simulation trajectory.

Results & Discussion

Structural analysis

Prediction of secondary structure of 2019-nCoV S-protein has been done using SOPMA (Self Optimised Prediction Method with Alignment). The S-protein contains 1288 aa residues comprising 350 α helices (27.17%), 312 β-turns (9.08%), 509 random coils (39.52%). Through ExPASyProtParam, the total number of negatively charged (Asp + Glu) and positively charged residues (Arg + Lys) were determined to be 112 and 100, respectively. The aliphatic index was found to be 81.58. The GRAVY (Grand Average of Hydropathicity) scored to −0.163. The instability index was computed to be 31.58. These features classify the protein as stable. It was also revealed through computational studies that the half-life of S-protein is maximum in case of mammals (mammalian reticulocytes- 30 hours) than in case of yeast (> 20 hours) and bacteria (E. Coli- >10 hours).

Structure alignment

Superimposition of structures of S-proteins of 2019-nCoV and SARS-CoV was evaluated by TM-align (https://zhanglab.ccmb.med.umich.edu/TM-align/) for comparative structural studies. These two viruses were considered for Structure-Structure superimposition due to maximum sequence similarity. From this study, it was observed through structural alignment that2019-nCoV and SARS-CoV only differ in RBD fragment and remaining part of the structure is identical (Suppl. fig. S2). From the structure alignment and phylogenetic analysis, it was observed that SARS-CoV is an ancestor of the newly upsurge virus 2019-nCoV. However, some changes were observed in the RBD fragment of 2019-nCoV compared to SARS-CoV.

Phylogenetic analysis

2019-nCoV shares the highest sequence identity (73.9095 %) with SARS-CoV and the lowest similarity in amino acid sequence was observed with HCoV−229E (10.6077 %).Similarly, the sequence identity is intermediate i.e 22.9037 % and18.5559 % with MERS-CoV, HCoV-

NL63, respectively. Phylogenetic tree in (Suppl. Fig. S3) shows that 2019-nCoV and SARS- CoV have same OTU (Operational Taxonomic Unit) due to the highest sequence similarity.

Molecular docking analysis

The binding modes of curcumin and catechin with S-protein and ACE2 were studied through AutodockVina1.1.2.The binding energy of S-protein with catechin and curcumin scored to be–10.5Kcal/mol and –7.9Kcal/molrespectively (Table1). The binding affinity of curcumin with ACE2 was noted to be –7.8Kcal/mol where as that of catechin was found to be - 8.9Kcal/mol (Table 2). From the docking scores, it can be deduced that both catechin and curcumin have strong binding affinity with S-protein as well as ACE2.AlthoughVan der Waals force, conventional hydrogen bonds and carbon hydrogen bonds facilitates binding between ligands (curcumin or catechin) and S-protein, amino acid residues of the protein that participate for such interactions for different bonds varies between curcumin and catechin (Fig. 2 and 3). Molecular docking experiments showed the affinity or binding capacity of curcumin and catechin with S-protein as well as ACE2. It also provided the evidence that catechin binds with greater affinity than curcumin

Molecular Simulation analysis

The results from Molecular Simulation data throw a light on the interaction of curcumin with S-protein. It was observed that interaction between curcumin and S-protein existed over the time span of 100ns but substantial interaction was seen during the simulation time of 40ns to 100ns (Fig. 4). Local changes along the protein chain were characterised through Root Mean Square Fluctuation (RMSF). The plot indicates curcumin possesses the ability to cause fluctuation of all amino acids of S protein (Suppl Fig. S4).Protein and ligand interaction was strong at RBD site of S-protein from 40ns to 90ns (Suppl. Fig. S6). RBD site of S-protein are

linked with keto group of curcumin with strong affinity at amino acid Leu–335 through hydrophobic bonds. Interaction with this amino acid occurs for 40% of the simulation time (Fig. 5).Molecular simulation studies favour docking studies which state that even though catechin has high binding energy with S-protein, curcumin binds directly to the RBD of the S-protein with greater affinity. At the same time, catechin is seen to cause greater fluctuation in amino acids near the RBD site.

The RBD fragment of 2019-nCoV spans from 319–591 S-residues[25]. From our studies it is deduced that curcumin directly binds to amino acids in this region Leu C:546, Gly C:548, Phe C:541, Asp C:571, Ala C:570, Thr C:572, Thr C:547, Thr C:573 whereascatechin binds to the S-protein in the near proximity of RBD fragment to Gln B:314, Glu B:309, Lys B:310, Gly B:311, Lys B:304, Tyr B:313, Thr B:302, Ile B:312, Leu B:303 and Ile B:312 residues (Table1).

The average change in displacement of atoms in all frames was recorded through Root Mean Square Deviation (RMSD).The average RMSD is obtainedto be 18 Å and 10 Å for S-protein- CurcuminandS-

protein- catechin complex respectively. RMSD plot depicted thebinding RMSD plot depicted theinteraction of S-protein andcatechinwhich indicate their rigid interaction between 10–20ns simulation time out of 100ns trajectory(Fig. 6). Maximum structural fluctuation of S-protein was observed in between 300–500 amino acids and after 1000 amino acids residues (Suppl Fig. S5). The above data supports that S-protein and catechin interaction occurs with amino acids of S-protein near the RBD site (319 aa–591 aa)[25]. Amino acid residues Arg–634 and Val–635 near the RBD site of S-protein have stronger affinity towards hydroxyl group of catechin with 54% and 35%,respectively, out of 100ns simulation trajectory (Suppl. Fig. S7).

The binding affinity of curcumin with ACE2 was noted to be –7.8Kcal/mol where as that of catechin was found to be –8.9Kcal/mol. The binding of curcuminor catechinwith ACE2 includes conventional hydrogen Bond, carbon-hydrogen bond and Pi-Sigma interactions. The amino acid residues of the protein that take part in above interaction vary for both ligands (Suppl. Fig. S8 and S9, Table.2).

These results depicted that curcumin and catechin bind to S- protein at the site where it was known to get involved in host cell binding. Similarly, it was also seen that these molecules attach to those sites of ACE2 which were involved in serving a medium of viral entry. Thus, it is apparent from the present study that viral infection can be prevented by use of curcumin and catechin. This would rather serve dual inhibitory machinery by blocking host cell receptor to virus and viral protein entry. Moreover, these two polyphenols (Curcumin an catechin) are potent immuno stimulant and have been reported to induce autophagy, another important mechanism of viral clearance[13,26]. Therefore, availability of curcumin and catechin may facilitate all different mechanisms simultaneously and thereby promote elimination or neutralisation of viral infection.

Conclusion

The pandemic novel corona virus has created a stark landscape in the social, health and economic sphere. The lethality of the virus has taken many lives. There is urgency to curb the widespread outbreak of 2019-nCoV. Our research via insilico approach indicates that curcumin and catechin can be used as potential moleculesto develop drugs to prevent the viral infection.

Declarations

Acknowledgements

Authors are thankful to the World Bank-OHEPEE for supporting Centre of Excellence in Integrated in Omics and Computational Biology, Utkal University. Support from DBT Government of India, New Delhi to Department of Biotechnology, Utkal University is gratefully acknowledged. Authors are grateful to the honourable Vice chancellor, Utkal University for his inspiration to develop this manuscript. We are thankful to Mr. Vinod Devaraji, Application Scientist, schrodinger, India for his inputs.

Conflict of Interest: Authors declare no conflict of interest.

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Tables

Table: 1; The binding energy, types of Interaction and amino acids involved in interaction in S-Protein of 2019-nCoV with Curcumin and Catechine.

Protein	Ligand	Binding Affinity	Interaction	AA: Name; ChainName; AA: No;
S-protein	Curcumin	-7.9	Vanderwaals:	Leu C:546, Gly C:548, Phe C:541, Asn A:856, Leu A:997, Ser A:967, Asp C:571, Ala C:570, Val A:976, Thr C:572
			Conventional Hydrogen Bond:	Asp A:979, Thr C:547, Arg A:1000, Ser A:975
			Carbon- Hydrogen Bond:	Thr C:573, Asn A:978, Cys A:743
			Pi-Donor Hydrogen Bond:	Thr C:573, Asn A:978, Cys A:743
			Pi- Sigma:	Leu A:966
S-protein	Catechine	-10.5	Vanderwaals:	Gln B:314, Glu B:309, Lys B:310, Gly B:311, Ile B:664, Lys C:733, Leu C:861, Asp B:950, Gly C:769, Ala C:766, Lys B:304, Thr C:761
			Conventional Hydrogen Bond:	Tyr B:313, Thr C:768, Asn C:764, Thr B:302, Gln B:954, Asp C:775
			Carbon-Hydrogen Bond:	Ile B:312
			Pi- Sigma:	Thr C:768, Val C:772, Leu B:303
			Pi-Cation:	Arg C:765
			Pi-Alkyl:	Ile B:312, Pro B:665, Arg C:765

Table: 2; The binding energy, types of Interaction and amino acids involved in interaction in Human ACE-2 receptor with Curcumin and Catechine.

Receptor	Ligand	Binding Affinity	Interaction	AA: Name; ChainName; AA: No;
ACE2	Curcumin	-7.8	Conventional Hydrogen Bond:	Gln A:102, Trp A:566
			Carbon-Hydrogen Bond:	Gln A:98
			Pi-Alkyl:	Val A:209, Pro A:565, Val A:212
			Pi-Sigma:	Leu A:95
ACE2	Catechine	-8.9	Conventional Hydrogen Bond:	Ser A:43, Asp A:382
			Carbon-Hydrogen Bond:	His A:401, Trp A:69, Ser A:47
			Pi-Alkyl:	Met A:62, Arg A:393
			Pi-Pi stacked:	His A:401, Phe A:390, Phe A:40
			Pi-Pi T-shaped:	His A:401, Phe A:390, Phe A:40
			Unfavourable Donor-Donor:	Arg A:393

Figures

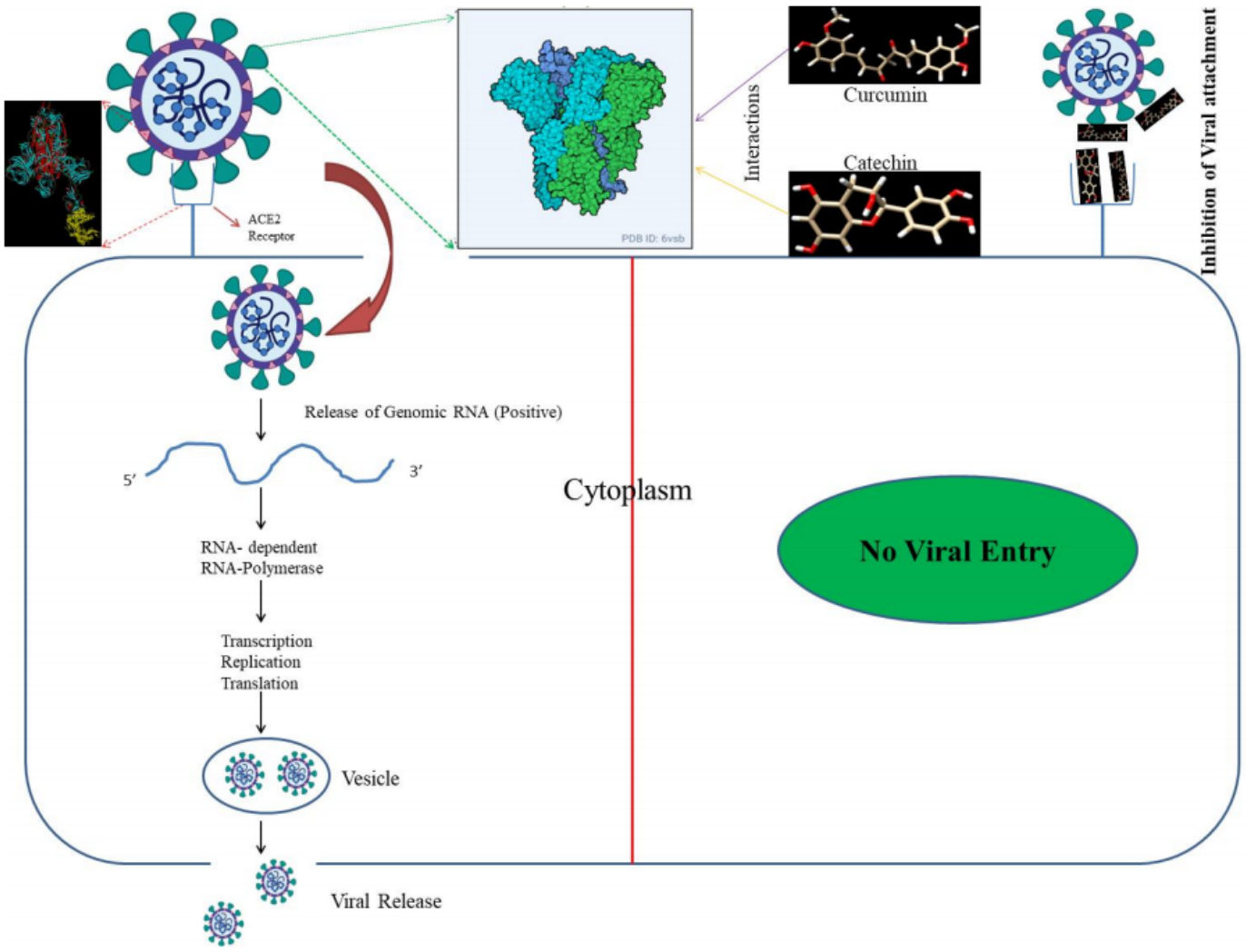

Figure 1

Binding of viral S-protein with the ACE2 cellular receptor.

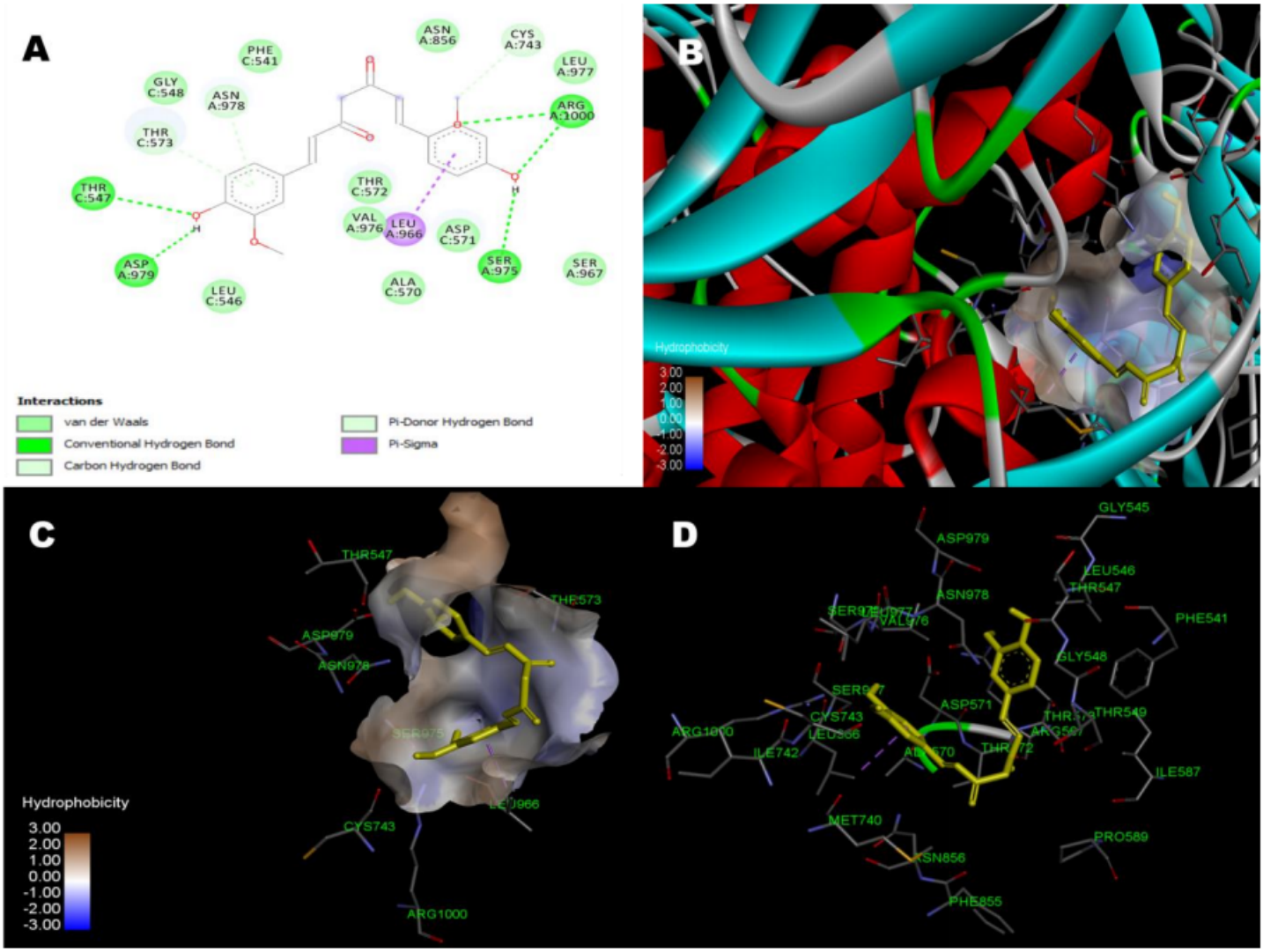

Figure 2

Docked pose of Curcumin in the binding pocket of S-Protein. (a) 2D representation of Curcumin and S-Protein interaction. (b,c) Curcumin bind with S- Protein in Hydrophobic condition. (d) Participating Amino acids in binding pocket of S- Protein.

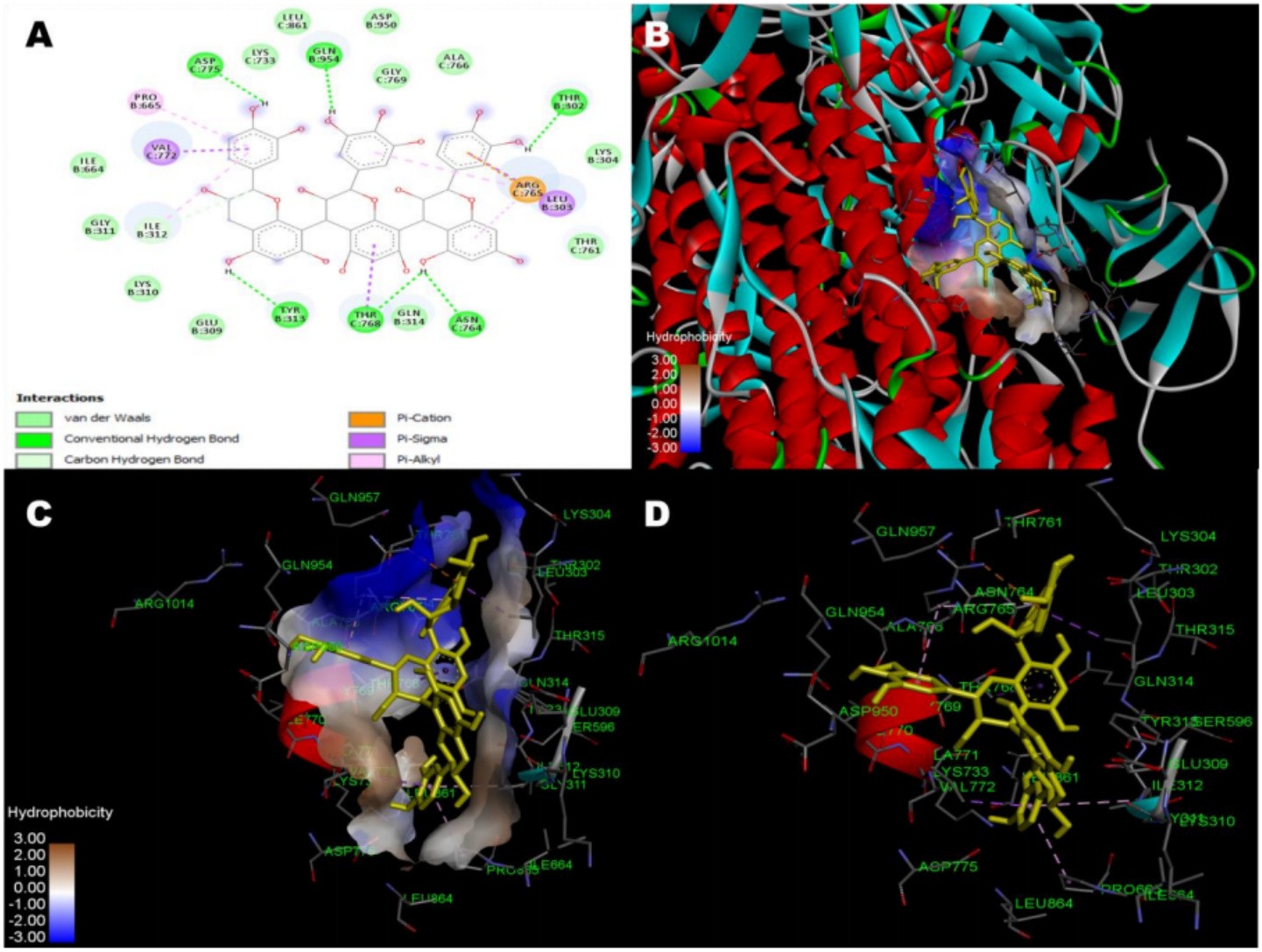

Figure 3

Docked pose of Catechin in the binding pocket of S-Protein. (a) 2D representation of Catechin and S-Protein interaction. (b,c) Catechin bind with S- Protein in Hydrophobic condition. (d) Participating Amino acids in binding pocket of S- Protein.

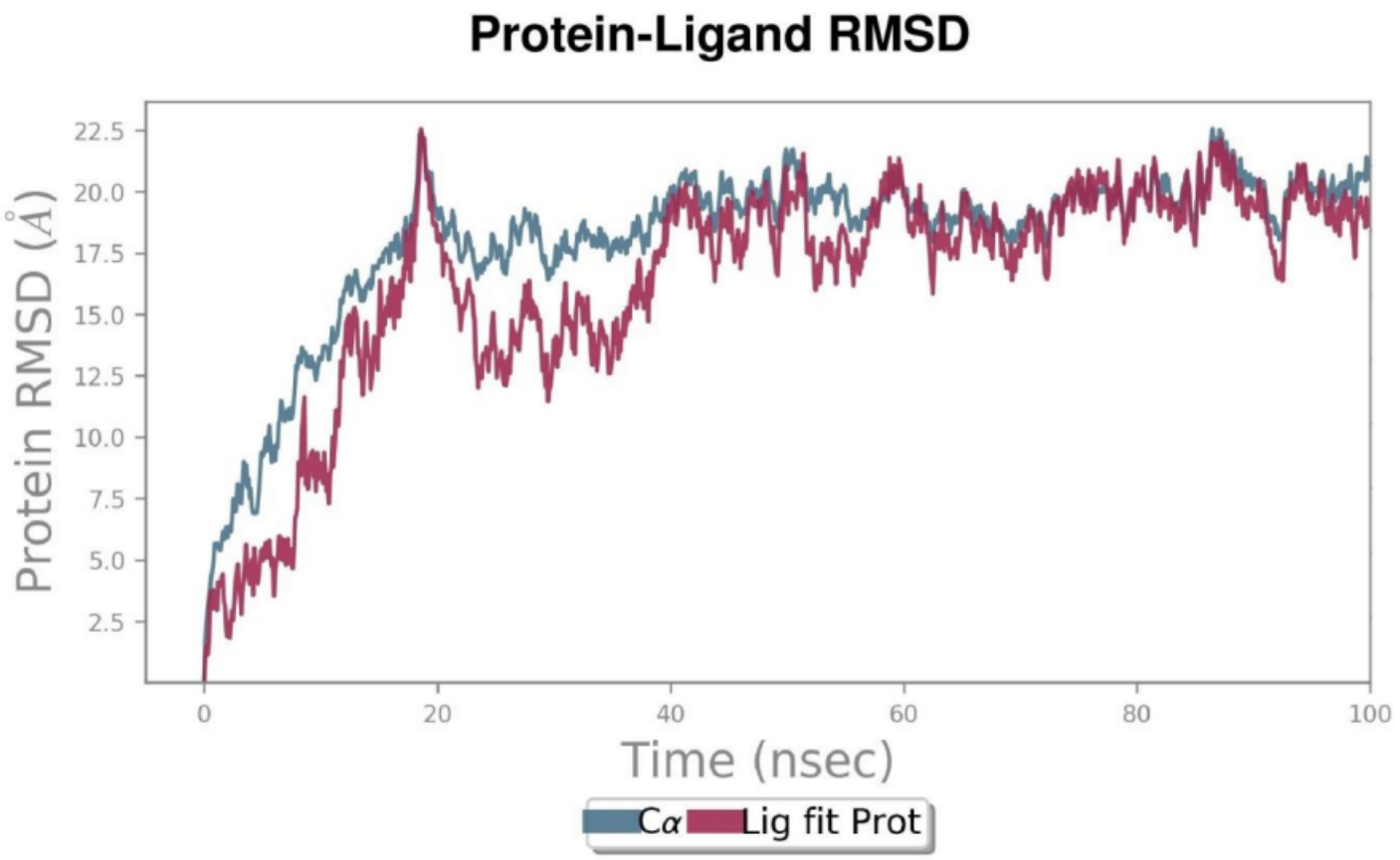

Figure 4

Root Mean Square Deviation (RMSD) plot for interactive complex of Curcumin and S- Protein during 0 – 100 ns of molecular dynamic simulation.

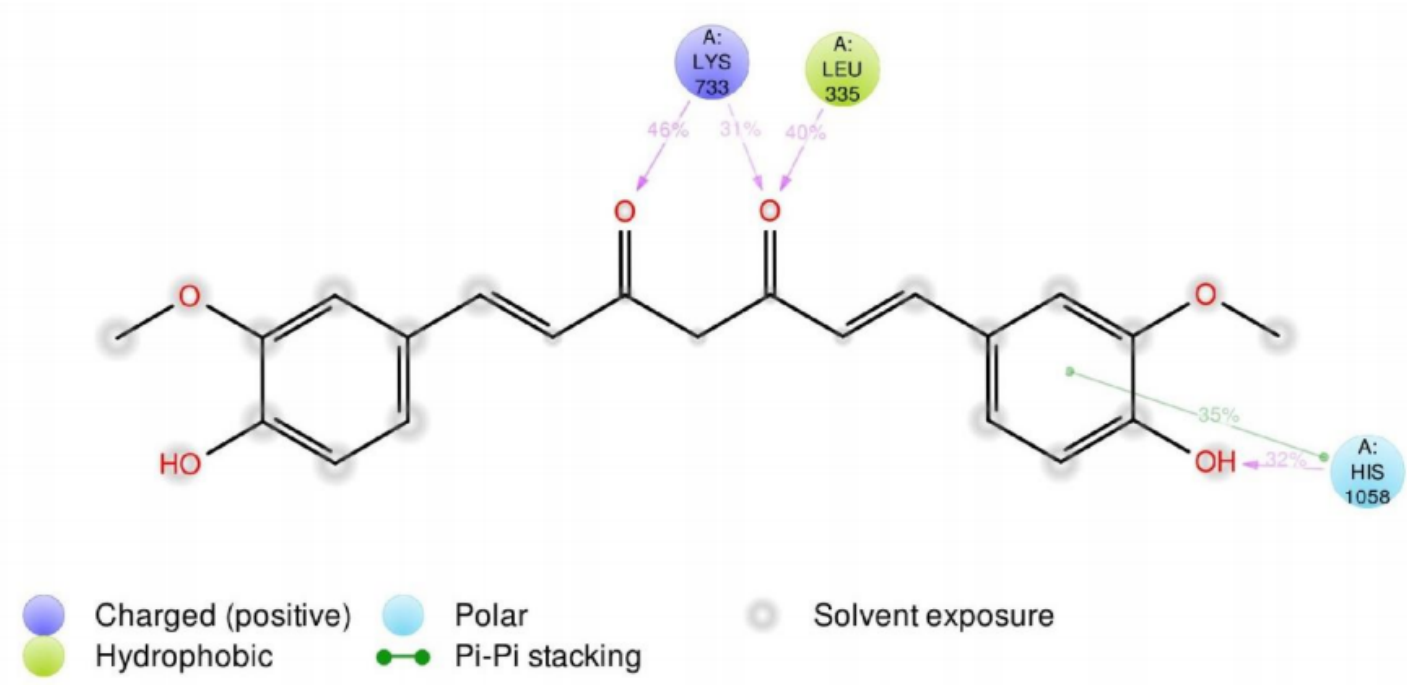

Figure 5

Illustration of bonds between Amino acid residues of S-Protein and Curcumin during their interaction.

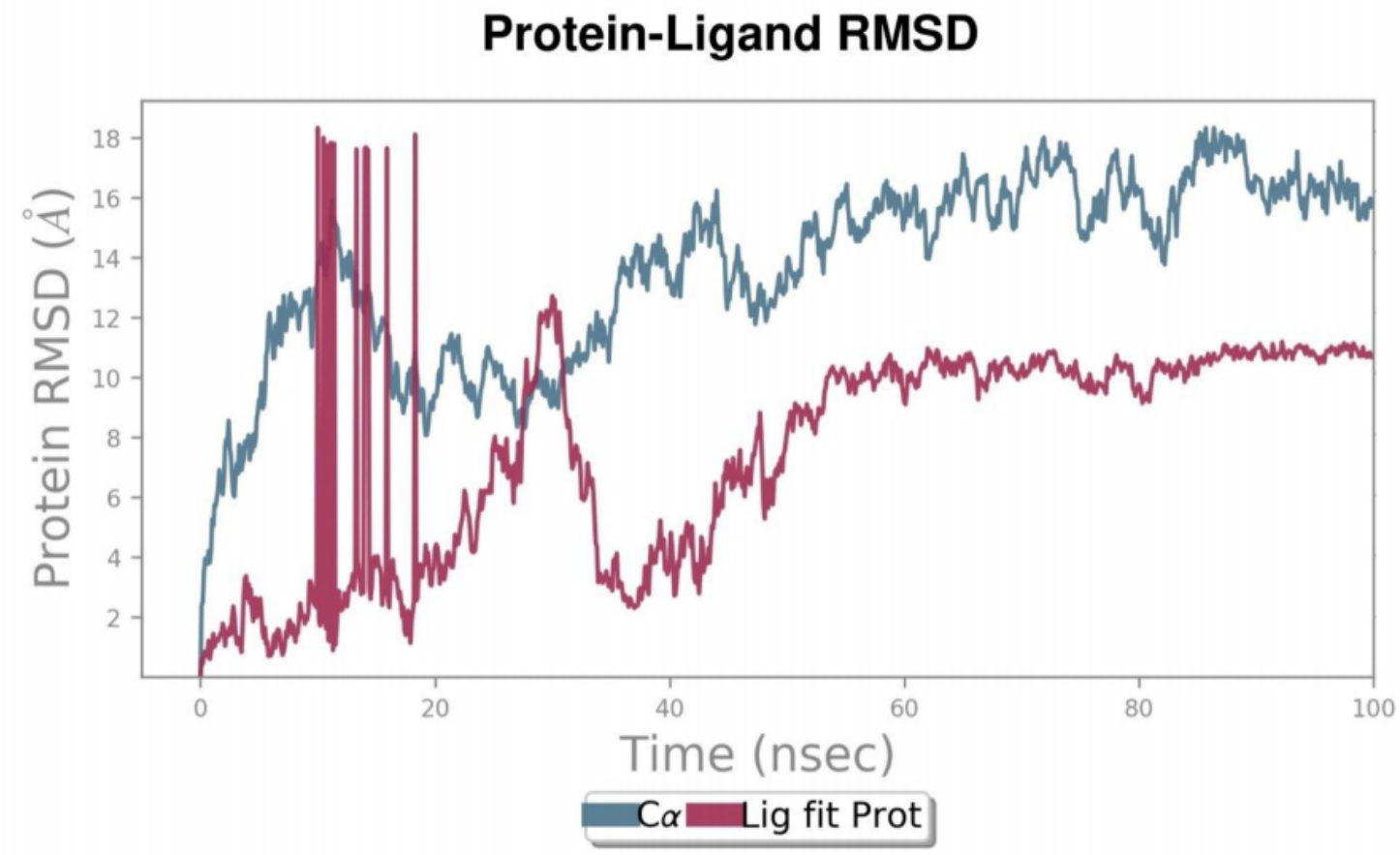

Figure 6

Root Mean Square Deviation (RMSD) plot for interactive complex of Catechin and S- Protein during 0 – 100 ns of molecular dynamic simulation.

Supplementary Files

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- Supplementaryinformation.pdf